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Clinical Proceedings

CHILDREN'S HOSPITAL

OF THE DISTRICT OF COLUMBIA

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Clinical Proceedings

CHILDREN'S HOSPITAL WASHINGTON, D.C.

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Placental Transfer and the Baby*

JOSEPH DANCIS, M.D.†

Our knowledge of placental physiology may be considered to begin with Harvey, the genius who first described the blood circulation. Harvey examined the placenta anatomically and made one of those fascinating jumps of which geniuses are capable in suggesting that the maternal circulation and the fetal circulation are distinct. It was a long time before scientists following in his path could prove the point that he suggested. With this point settled, it became obvious that there must be a mechanism for passing materials back and forth between the two circulations. It was quite natural in examining the placenta to think of it as a passive, sieve-like organ which lets little things through and stops big things. This thinking still permeates the medical field in spite of a large amount of evidence to the contrary.

With the development of analytical techniques, it became common practice to measure the blood concentrations of various materials in the fetal and maternal circulations and attempt to deduce placental function from their relative values. Despite the hazards of this reasoning, much useful information was gathered. It was learned, for example, that antibodies are often found in high concentration in the fetal circulation and it was realized that these antibodies must derive from the maternal circulation. This posed a problem for the sieve concept because antibodies are proteins and it was difficult to reconcile the passage of such large molecules with a barrier that also impedes the passage of a substance as small as sucrose. The possibility of a special mechanism for the transfer of antibodies had to be considered. Further evidence that a specific mechanism existed was provided by the observation that some antibodies were transferred more efficiently than others and that this was not consistently related to molecular size.‡ A clear-cut demonstration of this has been provided by

* Presented as part of Postgraduate Course, Children's Hospital, May 18–20, 1960.

† Professor of Pediatrics, New York University.

‡ An interesting table has been prepared by Vahlquist[1] of the relative titres of a large number of antibodies in maternal and cord blood in the human.

experiments in which heterologous antibodies (antibodies prepared in another species) and homologous antibodies have been injected into pregnant animals and the latter appeared in the fetal circulation in higher titre than the former, even though their molecular weight was larger.[2]

So far the study of protein transfer had been limited to that of antibodies because antibodies were the only available protein "tracer." With the advent of radioactive techniques it was possible to follow the transfer of other plasma proteins. It then became evident that the transfer of proteins across the placenta was not limited to trace amounts of antibodies but that much larger amounts of gamma globulin, albumin, and certain other globulins crossed the placenta.[3]

I have consistently referred to the transfer of proteins from mother to child as "transfer across the placenta." This route of transfer was generally accepted as so obvious as to require no proof. In fact, years ago a correlation was noted between the thickness of the placenta in various animal species and the titre of passively transferred antibodies in the fetal circulation—the fewer the cellular layers that the placenta interposed between the maternal and fetal circulations the more efficient the transfer of antibodies. Thus the "thin placentas" of the rabbit, guinea pig, and man passed proteins through easily whereas the "thick placentas" of the horse and sow did not. This coincided with the sieve concept of placental function.

It took the keen scepticism of Brambell and his colleagues[2] first to raise the question and then to demonstrate that antibodies do not cross the placenta at all in the rabbit and guinea pig. Instead they take a roundabout route from the maternal circulation into the uterine cavity and then through an everted yolk sac peculiar to rodents and finally into the fetal circulation. The transfer of antibodies was not the result of the thinness of the placenta at all. With this same refreshing scepticism, Brambell suggested that the transfer of antibodies in the human might be not across the placenta but through the amniotic fluid. It is with some relief that I can report, some years after the original suggestion, that the placental transfer of antibodies in the human does indeed occur across the placenta.

The mechanism by which this transfer occurs and how it is rendered selective remain problems for the future. Electron microscopists have given us a morphological picture of the process. They have described an active engulfing of particles by micro-villi of the cell wall and have called it "pinocytosis." We must await a biochemical explanation of the selectivity.

So much for the transfer of large molecules. What about substances of small molecular weight? Investigators in the past had noted that monosaccharides, like glucose, passed through the placenta readily while di-

saccharides, like sucrose, did not. Since one has twice the molecular weight of the other, an obvious conclusion was that this was a matter of size. Reinvestigation of the problem has turned up other observations that do not fit this simple hypothesis. To mention but one, the transfer of D-xylose is regularly two to three times that of L-xylose even though these substances are of identical size but simply mirror images of each other.[4] The same is true with amino acids, in this instance the L-form being more readily transferred than the D-form. And so, even with these small molecules a simple passive role cannot be assigned to the placenta.

In considering the interrelations of placenta and baby, it is reasonable to turn to the modifications that intrauterine existence impose on fetal metabolism. It has been a common practice in the past to compare fetal metabolism with that of the adult and assume that differences represent inadequacies on the part of the fetus. While it is true that many of these differences represent inadequacies for an organism faced with extrauterine problems, many must also be of distinct advantage to an intrauterine fetus.

An example of this was noted in the placental transfer of estrogens. Estrogens are very soluble in organic solvents, but poorly soluble in water. After birth, in order to excrete estrogens into the urine, they must first be rendered water-soluble by being conjugated with glucuronic acid.

When we approached the problem of placental transfer, we naively drew a parallel with renal excretion and assumed that the glucuronidated material would cross the placenta and the unconjugated estrogens would not. In fact, we found exactly the reverse.[5]

When we re-examined the problem in the light of these new observations, it all made very good sense. It is known that the fetus is a very poor conjugator. This has been well documented for bilirubin. It is simple to understand the advantage to the fetus of not conjugating materials before birth if this would represent an obstacle to placental transfer and excretion. However, after birth the capacity to glucuronidate must rapidly develop to facilitate excretion through the kidney.

To return to the placenta, just how effectively does the placenta serve as a protective barrier for the fetus? Table 1 contains a partial list of the

TABLE 1

Medications Transferred Across the Placenta

Antibiotics	Sulfonamides, Penicillin, Chloramphenicol, Streptomycin, Oxytetracycline, Erythromycin.
Sedatives	Morphine, Scopolamine, Paraldehyde, Chloral Hydrate, Barbiturates.
Miscellaneous	Atropine, Salicylic Acid, Digitoxin, Ephedrine, Iodides.

TABLE 2

*Human Intrauterine Infections**

Transplacental Route Demonstrated	Bacteria:	Pneumococcus, *Bacillus anthracis*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Pasteurella tularensis*, *Treponema pallidum*
Transplacental Route Probably	Bacteria:	Streptococcus, Salmonella, Shigella, *Vibrio cholera*, Brucella, *Treponema pertenue*, Leptospira, Borrelia, Listeria
	Viruses:	Rubella (?), Rubeola, Variola, Varicella, Poliomyelitis, Encephalitis lethargica
	Protozoa:	Malaria, Toxoplasma
Extraplacental	Bacteria:	Staphylococcus, Gonococcus, Corynebacterium
	Viruses:	Herpes zoster, Inclusion blenorrhea

* Modified from table 29 from Le Placenta Humain, by Professeur Jean Snoeck, Masson et Cie, Paris.

medications that will cross the placenta with facility, some to the benefit of the fetus and some to its disadvantage. The permeability of the placenta to penicillin was a great advantage when syphilis was prevalent, so that fetal syphilis could be cured at the same time as the maternal disease. But the placental transfer of long-acting sulfonamides may represent a hazard in potentiating kernicterus.

In table 2 is a list of infections which can affect the fetus. There are three groups—one in which a transplacental route has been well validated, one in which it is probable, and a third in which transmission is extraplacental usually through the amniotic sac. How do microorganisms get through the placenta? It is not likely that there are selective mechanisms to carry them across. Another observation supplies a reasonable explanation. Douglas and associates[6] have been studying the frequency with which placental cells are shed into the maternal circulation. By inserting catheters into the uterine veins and withdrawing blood samples, these investigators have demonstrated that large numbers of these cells are constantly breaking off into the maternal circulation and floating away. The covering of the fetal capillary in the placenta is very thin and it is not difficult to imagine that such activity would permit temporary small communications between the two circulations. If this occurred at an appropriate time when organisms were present in the maternal blood, they might find their way across into the fetal circulation. Of course, a more obvious mechanism for transfer exists when there is evident local pathology in the placenta.

What then is our current concept of the placenta and the manner in which it fulfills its many obligations to the fetus? On the one hand, it is

not so effective a barrier as we once believed. Plasma proteins, microorganisms and even red blood cells penetrate the barrier with regularity though not in large amounts. On the other hand substances of small molecular weight like carbohydrates and amino acids do not simply drift across through a sieve-like structure, but are helped across by placental activity. As our knowledge of the placenta increases, it becomes more complex and more remarkable—an intricate organ well worthy of study and respect.

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Helminthic Disease and Anthelminthic Drugs*

Henry K. Beye, M.D.†

As is well known, there are two types of helminths, the round and the flat worms. According to Belding,[1] there are 14 species of round worms or nematodes, 6 species of cestodes or tapeworms, and 10 species of trematodes or flukes of major importance in human disease. These various species and their associated diseases can be classified into three categories.

The first includes those parasites which are relatively common in the

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United States. In this category are pinworms, *Enterobius vermicularis;* whipworms, *Trichuris trichiura;* intestinal round worms, *Ascaris lumbricoides* and *Strongyloides stercoralis;* and hookworms and tapeworms, primarily *Taenia saginata.* The second category includes those parasites causing syndromes which are encountered less frequently in the United States, such as visceral and cutaneous larva migrans, tropical eosinophilia, schistosomiasis, swimmer's itch, Echinococcus disease and trichinosis. In the third category are the more exotic conditions which might be encountered only on a few occasions in a pediatric practice in the United States. This does not decrease their importance, especially now that, figuratively, the world is smaller than in the past. Filariasis and liver fluke infections are in this category.

One should not underestimate the influence of the parasite load on the peoples of the world. Stoll[2] estimated the number of people infected with *Enterobius vermicularis* (pinworm) to be 208 million; hookworm, 456 million; *Ascaris lumbricoides*, 644 million; *Trichuris trichiura*, 355 million; *Strongyloides stercoralis*, 35 million; *Taenia saginata*, 39 million; *Taenia solium*, 2.5 million; *Trichinella spiralis*, 28 million; and the three Schistomsomes, *japonicum*, *haematobium*, and *mansoni*, 114 million. The various types of human filarial parasites account for infections in an estimated 300 million persons. Because increased irrigation and land development may cause an increase in the spread of schistosomiasis, the prevalence estimate of Stoll for this disease is believed to be low.

Clinical manifestations and symptomatologies vary from species to species, race to race, and place to place, but can be correlated to the life cycles of the worms and host reactions to the various forms of the parasite. For example, the life cycle of those round worms which pass most of their adult life in the gastrointestinal tract can be divided into two general groups; those in which larval forms migrate outside the gastrointestinal tract and those in which the larval forms do not migrate. The larvae of *Ascaris lumbricoides*, *Strongyloides stercoralis*, hookworm, and *Trichinella spiralis* penetrate through the skin or through the walls of the small intestine and subsequently they pass through the inferior vena cava, the right heart, and the pulmonary circulation, and finally through the alveolus, the bronchus, the trachea, pharynx, and esophagus to the stomach and small intestine, where the adults then mature. While the larvae migrate along this route, transitory pneumonitis, eosinophilia and fevers sometimes become manifest. Infective larvae of *Strongyloides stercoralis* and hookworm penetrate the skin, and at this site can cause pruritis, urticaria, and local skin reactions. *Enterobius vermicularis* and *Trichuris trichiura* develop within the intestinal tract.

In general, these parasites may cause injury by sporative action, com-

pression, trauma to the affected area, or toxin production. Each nematode is different in respect to the role of these mechanisms. For example, the symptoms of cutaneous larva migrans are caused by the cutaneous migration of the dog hookworm, *Ancylostoma brazilliense*, while those of visceral larva migrans, on the other hand, result from the more general migration of the dog ascarid, *Toxocara canis*, through the viscera of a human host. Following the ingestion of larvae of the dog ascarid by a child, usually a dirt eater, the larvae penetrate the wall of the small intestine and go first to the liver. In the liver they cause an eosinophilic granulomatous type of reaction. Frequently the larvae migrate to other areas in the body, particularly the central nervous system or the eyes. Clinically, these patients exhibit eosinophilia, hepatomegaly, hyperglobulinemia, intermittent fever, lung infiltrations, and occasionally neurological symptoms and deviations of behavior. Although *Toxocara canis* has definitely been associated with this condition, *Toxocara cati* is also a good possibility.

Another syndrome, tropical eosinophilia, is relatively common in some tropical areas. There is some reason to believe that this condition may be associated with a nonhuman filarial infection in some areas of the world. Transitory pneumonitis and eosinophilia are associated with any helminths which migrate through the lungs.

Those pediatricians practicing around the Great Lakes and in certain seacoast areas may see swimmer's itch. This condition is due to the penetration of the human skin by cercariae of schistosomes which ordinarily affect species other than human in their full cycle. Echinococcus disease is certainly common in Alaska and Canada where two forms, *Echinococcus multilocularis* and *Echinococcus granulosa*, have recently been shown to exist.

The third category of helminthic disease should not be entirely forgotten. Recently a student, vacationing in Florida, returned with a painful subcutaneous nodule on his arm. This, upon surgical removal and microdissection, revealed larvae of *Dirofilaria immitis*. Persons infected with *Wuchereria bancrofti* can certainly be found in the United States. Even though it is unlikely that such parasites would become established within the United States under present conditions, pediatricians should not exclude the possibility of filariasis in some of their differential diagnoses.

Goodman and Gilman,[3] in discussing anthelminthic drugs, write: "Many of the drugs still used today are therapeutic relics and highly toxic. New synthetic drugs are rapidly displacing the older empirical agents. Another important consideration in the selection of the anthelminthic is its cost. Many patients with helminthiasis are without adequate funds for medical treatment and must be treated in free clinics. Some of the older anthelminthics are most expensive."

Anthelminthics can be utilized from a number of points of view, depending on whether or not the pediatrician's main responsibility is to an infected individual child or to an infected community or population group. For example, in the United States emphasis is mainly on the infected child, but even at the turn of the present century, the approach was on a community basis in the hookworm campaign conducted by the Rockefeller Foundation. With the increased application of preventive medical programs in underdeveloped countries and with the development of more specific anthelminthics, the role of mass chemotherapy will become increasingly important. Methods of sterilizing the soil and even possibilities of immunization against helminthic infestations are receiving increasing attention.

Prior to 1947, standard anthelminthics consisted of carbon tetrachloride, tetrachlorethylene, hexylresorcinol, gentian violet, santonin, and others. An era of broad spectrum anthelminthics probably was ushered in by Hewitt and coworkers using diethylcarbamazine, a piperazine derivative, in clinical trials against *Wuchereria bancrofti* infections. Although the drug was first used to treat individuals, its greater application was for mass chemotherapy in the control of this filarial parasite. Subsequently, this drug was used for treatment of *Ascaris lumbricoides*, tropical eosinophilia, and other filarial parasites. Diethylcarbamazine is a relatively nontoxic drug, and is administered for filarial infections at a rate of 2 mg. per Kg. of body weight for from 7 to 30 days. In *Wuchereria bancrofti* infections, reactions to the drug are generally mild, and consist of a mild degree of fever for one or two days, and nausea and vomiting; more severe reactions have occasionally been reported. Diethylcarbamazine has been reported by some to be effective against cutaneous larva migrans.

The piperazine salts, especially the citrate marketed mainly as a syrup containing 100 mg. of piperazine per ml., have shown good anthelminthic activity. This drug is especially effective against pinworms and ascaris. Another anthelminthic, dithiazanine iodide, was reported by Swartzwelder et al.[4] and others as being especially effective against whipworm infestations and strongyloidiasis. This drug was likewise observed to be active against ascaris and pinworms. Dosage schedules have ranged from 200 mg. three times a day for from 5 to 21 days in strongyloidiasis and trichuriasis to 100 mg. twice a day for pinworms. The drug is less effective against hookworm and tapeworm infestations. Nausea and, sometimes, vomiting seem to be a fairly frequent reaction to the drug; diarrhea is more frequently observed in children. To the author's knowledge, no other reactions have been reported.

In the latter part of 1958, Young et al.[5] reported that bephenium was found to exert significant effects against human hookworm. This drug is now used in 5 Gm. doses in the treatment of hookworm.

The common helminthic conditions and therapy recommended by Swartzwelder and Frye[6] can be summarized as follows:

1. *Ascariasis: Uncomplicated intestinal*—Piperazine citrate—initial dose of 150 mg. per Kg. of body weight with maximum of 3 Gm. Repeat with another single dose at one week. Fasting and purgation are unnecessary.

Partial intestinal obstruction—Although complete intestinal obstruction due to ascariasis still requires surgical intervention, partial intestinal obstruction responds to conservative measures of abdominal decompression and the maintenance of fluid and electrolytic balance, supplemented by piperazine citrate syrup. The following measures are those recommended by Swartzwelder and Frye.

a) Parenteral fluids are administered as required.

b) Wangensteen drainage with a Levin tube is employed for abdominal decompression to relieve distention and vomiting if necessary.

c) Physiologic saline enemas are given promptly to remove any worms which may have collected in the large bowel.

d) After four to six hours of nasogastric suction, the vomiting usually abates and piperazine citrate syrup is instilled by gravity through the drainage tube. Suction is discontinued during, and for one to two hours after, administration of the drug. The initial dose of piperazine citrate is 150 mg. per Kg. of body weight with a maximum of 3 Gm. (30 ml. of the syrup). Subsequently, 65 mg. of piperazine citrate per Kg. of body weight with a maximum of 1 Gm. (10 ml.) is given at 12 hour intervals for six doses.

e) After the acute illness has subsided the stools should be examined. If eggs of *Ascaris lumbricoides* are present, the residual infection should be treated with piperazine as in an uncomplicated case of intestinal ascariasis.

2. *Trichuriasis:* Dithiazanine iodide—10 mg. per Kg. of body weight per day for from 5 to 15 days.

3. *Hookworm:* Bephenium hydroxynaphthoate—5 Gm. dissolved in half a glass of water given orally as a single dose. An alternative is tetrachlorethylene provided the patient does not also have ascariasis.

4. *Strongyloides:* Dithiazanine iodide—100 mg. three times daily after meals for 21 days.

5. *Enterobiasis:* Piperazine citrate—65 mg. per Kg. of body weight with a maximum of 2 Gm. per day in a single daily dose for six consecutive days. The entire family should be treated. Dithiazanine iodide in a dosage of 100 mg. three times a day after meals for five days for adults, and 10 mg. per Kg. of body weight per day in divided doses for five days in children is also effective.

6. *Tapeworm:* Quinacrine hydrochloride (Atabrine), orally or by duodenal intubation, is effective against the large tapeworms. In the author's

experience, transduodenal intubation and administration of quinacrine hydrochloride has been very effective. A Rehfuss tube is inserted into the upper duodenum, and its position verified by x-ray. Eight hundred mg. of quinacrine dissolved in 30 ml. of physiological saline is then administered through the tube. Thirty minutes later the patient is purged with 30 ml. of sodium sulfate solution via the tube.

An alternate method of oral administration of quinacrine hydrochloride is recommended by Swartzwelder to be given in one 100 mg. tablet every five minutes. The use of sodium bicarbonate in the water taken with the drug may obviate or minimize the nausea and vomiting in patients who do not tolerate quinacrine well.

SUMMARY

Some of the problems associated with helminths in the United States are briefly reviewed. Global parasitology is described, and some of the newer anthelminthics which have been developed in the past 10 years are discussed. New clinical syndromes caused by helminths are continually being more clearly described and understood. Relatively nontoxic and broad spectrum anthelminthics are contributing to an evolution in this area of medical science.

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Treatment of the Acute Asthmatic Attack in the Child

[Editor's note: The outline which follows has recently been proposed by the Department of Pediatric Allergy at Children's Hospital as providing the most useful approach toward relieving the acute asthmatic attack in children admitted to the hospital or seen in the Outpatient Department.]

While it is desirable *completely* to relieve an attack of asthma when first seen, this is sometimes impossible and often unnecessary. If *amelioration* of the attack can be accomplished by suitable means, and the patient sent home and followed up with suitable supportive medication, a period of 24 to 48 hours is frequently necessary for the patient to recover fully.

TREATMENT IN THE OUTPATIENT DEPARTMENT

1. A general physical examination should be performed for a complete assessment of the patient's condition, especially as regards severity of the attack, presence or absence of infection or dehydration, and any other factors which might influence the duration or severity of the asthma.

2. Most of these children are upset and excited. The child should be placed in the quietest cubicle available and left there for the duration of his outpatient treatment.

3. Give epinephrine solution 1:1000, 0.15–0.25 ml. subcutaneously, and if necessary, repeat every 15 to 20 minutes for three or four doses to judge maximum effect. If aqueous epinephrine appears satisfactory but the effect is too transitory, epinephrine suspension 1:200 (Susphrine®), 0.1–0.25 ml. subcutaneously may be used for its more prolonged effect. The effect of this drug may last up to 6 to 10 hours.

4. If presumed bacterial infection is present, broad-spectrum antibiotics or perhaps sulfonamides should be given. Penicillin, by mouth or by injection, may be used if a streptococcal infection is present or suspected, but probably is less desirable than the first two types of drugs for routine use, since sensitization reactions may occur.

5. If satisfactory results have been obtained from aqueous and/or suspended epinephrine, the patient may then be sent home with the following treatment:

   a. Nose drops if much nasal congestion is present.
   b. Bed rest and adequate fluids. The patient should not be allowed to return to school the following morning.
   c. Some preparation of ephedrine which may be taken by mouth should be given, such as syrup of ephedrine and elixir of phenobarbital in equal parts, one or two teaspoons per dose, or ephedrine and Amytal®

tablets or capsules. For more severe cases, Tedral® tablets or syrup may be used.

d. Antihistaminic treatment should *not* be used. One preparation of Tedral does contain an antihistamine and is called Tedral Anti-H.® This is not suitable for routine use in children.

6. If the child does not respond to aqueous or suspended epinephrine, he should be kept in the cubicle under observation and given the following:

a. Antibiotics if indicated.

b. Aminophylline in suppository form. With children one generally uses the half or quarter strength Aminet® suppository (the half strength suppository contains aminophylline 250 mg., and pentobarbital 50 mg.). The proper dose of aminophylline is extremely important. A dose of 3–6 mg. per Kg. of body weight as a single dose, however given, should never be exceeded and this drug should be repeated only when necessary at not less than 6-hour intervals.

c. Oral medication with one of the ephedrine preparations, as mentioned above, should also be given. This is more desirable than giving drugs combined in a suppository. One may then judge the effect of the drugs individually.

d. A minimum of one hour should be allowed for observation under these conditions.

7. If the patient shows complete or even partial relief on this regimen, it is perfectly safe to allow him to return home with instructions for continuing the medication. The child should be encouraged to drink large amounts of fluids, and if possible, the parents should keep the child in bed in a room as free of dust, cooking odors, animal danders, paint, tobacco smoke, etc., as possible. If convenient, the patient should return to the clinic the following day to evaluate results. A period of at least 12 to 48 hours should be allowed for full recovery to occur. It is also important that parents should be instructed not to give aminophylline suppositories by the clock, but only on specific indication, in order to avoid overdosage.

8. For patients in whom none of the above treatment results in any improvement, or in instances when the child's condition deteriorates under observation, hospitalization is advised and indicated since these children may truly be classed as being in status asthmaticus. Additional treatment is best carried out under hospital conditions.

HOSPITAL CARE

1. The child should be admitted to a single, quiet room, free from unnecessary noise and agitation, and as clean as possible. Personnel and visitors should not be allowed to wander in and out of the room any more than is absolutely necessary.

2. Some type of mild sedation may be necessary to allay apprehension if this is marked. Secobarbital (Seconal®), isoamylethyl barbituric acid (Amytal®), or other rapidly acting barbiturates are recommended. Slow acting phenobarbital or such respiratory depressants as morphine or Demerol® are not to be used.

3. Oxygen may be needed and should be used for the relief of restlessness and air hunger. Do not wait for the appearance of cyanosis. Oxygen should be moist and the temperature of the tent should never be lower than 75° F.

4. Oral and rectal medications previously used may be continued in the hospital.

5. Since these patients in status asthmaticus are often suffering from an acidosis and are dehydrated, intravenous fluids are nearly always indicated, and frequently are all that are required to terminate the attack. These fluids should always be given a chance to work before any other intravenous medication is planned. Improvement, again, may be gradual rather than dramatic, but lack of rapid response is not an indication for more heroic treatment. If the patient is improving steadily, nature should be allowed to take its course for the moment.

6. For the patient who fails to respond in any way to the above measures but instead appears to get worse, or who on admission appears to be in great distress, one or both of the following therapeutic measures may be employed.

a. *Hydrocortisone sodium succinate* (Solucortef®), 50–100 mg. intravenously, should be given and may be repeated in two to six hours if necessary. This material is much more prompt in its action than ACTH or the intramuscular corticoids, and may be all that is required to halt the severe attack. Prednisone 21-phosphate (Hydeltrasol®), 20–60 mg., may be used in like manner.

b. *Intravenous aminophylline.* This is a most useful but potentially dangerous drug, and should, except in the most extenuating circumstances, be given in the hospital. The dosage is 3–6 mg. per Kg. of body weight, given either as a direct intravenous injection requiring approximately 10 minutes to complete, or given in the intravenous fluids over a period of some 15 to 30 minutes. Toxic reactions to this drug are common, regardless of the method of administration, and include nausea, vomiting, hematemesis and melena. Acidosis may also occur. Occasionally, syncope and cyanosis may appear after only a small portion of the prescribed dose has been injected. This is considered to be an indication of idiosyncrasy to the drug, and when these symptoms appear, it should not be used again.

In general, it is felt that hydrocortisone sodium succinate is a safer drug to use and is sufficiently rapid-acting to produce the desired

therapeutic response. Aminophylline intravenously should be reserved for those instances where immediate action is necessary.

The patient who is given hydrocortisone sodium succinate as an emergency treatment must, after relief of his acute attack of asthma, be placed upon suitable dosage of oral adrenal cortical steroids for a period of two to five days in order to assure that there will be no recurrence of the asthmatic attack.

APPENDIX

Drugs of Use in the Treatment of the Acute Asthmatic Attack in the Child

Tedral Tablets:	
Phenobarbital	8 mg. (1/8 gr.)
Theophylline	130 mg. (2 gr.)
Ephedrine hydrochloride	24 mg. (3/8 gr.)
Tedral Ped. Suspension:	
Each teaspoonful—(5 cc.) contains:	
Phenobarbital	4 mg. (1/16 gr.)
Theophylline	65 mg. (1 gr.)
Ephedrine hydrochloride	12 mg. (3/16 gr.)
Quadrinal Tablets:	
Phenobarbital	24 mg. (3/8 gr.)
Theophylline (calcium salicylate)	120 mg. (2 gr.)
Ephedrine hydrochloride	24 mg. (3/8 gr.)
Potassium iodide	0.3 Gm. (5 gr.)
Quadrinal Suspension:	
Contains in each 5 cc.:	
Phenobarbital	12 mg. (3/16 gr.)
Theophylline (calcium salicylate)	65 mg. (1 gr.)
Ephedrine hydrochloride	12 mg. (3/16 gr.)
Potassium iodide	160 mg. (2½ gr.)
Aminet Suppositories:	
Half Strength:	
Pentobarbital sodium	0.05 Gm.
Aminophylline	0.25 Gm.
Benzocaine	0.03 Gm.
Quarter Strength:	
Pentobarbital sodium	0.025 Gm.
Aminophylline	0.125 Gm.
Benzocaine	0.015 Gm.

The Long-Range Management of Asthma in Children

RICHARD H. TODD, M.D.*

When is a child to be considered asthmatic? Certainly many children have one or two wheezing episodes associated with respiratory infections in infancy; some of these children never have another attack. I believe, however, that if a child has three or four "asthmatic" attacks, the wheezing is no longer a symptom but is evidence of a disease; such a child is then considered to be an asthmatic child. Another child may have had infantile eczema for a year or so and then develop an asthmatic attack; we can be fairly certain that this child is going to have a number of asthmatic attacks, and he is classified as an asthmatic child after only one attack. The same is also true of a child suffering from allergic rhinitis who has his first attack of asthma.

After a diagnosis of asthma has been reasonably established, what steps must we take in its management? First we must apprise both the child and his parents what asthma really means. We must gain the confidence of the parents; they must have faith in their physician. They must have some knowledge of the disease so that they understand that it is not a fatal disease but instead is often a long drawn out illness in which it is necessary to provide constant observation and care and a few extra niceties which the average child does not get. It is also certainly very easy to make these children believe that they are "different" from the average child; this is what we must attempt not to do, and yet, at the same time, we must protect them against certain everyday hazards. They must understand that their stamina at times will not be comparable to that of their fellows. They may not be able to run as far or as hard as some of their friends; consequently they probably will not be as good as football players and track men as some of their friends. Therefore they should be directed into fields of endeavor which are not too taxing on their respiratory systems. It is well to build up their self-confidence, and we can do that by steering them into such hobbies as riflery or archery; or we can encourage them to jump, or throw the javelin or discus rather than compete in the 100 yard dash. It is good for them to try to do the best they can in competition, but it is important that they not be discouraged if they cannot do as well as their confreres.

There are a few things such as weather conditions which affect the asthmatic adversely; he does not tolerate cold weather as well, and con-

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sequently should wear a hat and have his knees covered in spite of the fashions which are prevalent at the time. It is also better, when he jumps out of bed in the morning, if he does not jump onto a cold floor; this will often precipitate an attack. It is wise either to have him wear socks all night, or have a throw rug placed at the side of his bed onto which he can jump rather than the cold floor. The rooms should not be allowed to get too cold at night; perhaps 65 degrees should be the lower limit. The air should be heated before it is allowed to enter the room; the windows of another room should be opened rather than the windows of his own room. This not only warms the air but also keeps any potential pollens less concentrated.

Preparing for his future may be a problem for the teenager who has suffered from asthma all his life. Such a patient certainly ought to be aware of the fact that there are some occupations that are better for him than others. Farming is a bad one because of the exposure to animal dander and grass and weed pollens; barns are usually filled with dust composed of grasses, animal hairs and molds which may often exacerbate the symptoms of a so-called cured asthmatic. Working with animals in such professions as veterinary surgery or animal husbandry, or even animal research may also become a hazardous occupation for him in his later years. Flour mills are notorious for starting old asthmatics back in the asthma groove again.

As in the treatment of any disease, the asthmatic child should be treated over-all; all defects, abnormalities and infections should be corrected. Anemia should be treated, and obesity should likewise be corrected since we think that the obese child has more severe attacks of asthma than the comparable asthmatic child who is thin. What about the question of tonsillectomy and adenoidectomy for the asthmatic child? In our experience the tonsillectomy done just to cure asthma often makes it worse; tonsillectomy may even precipitate the first attack of asthma. As in non-allergic diseases, the only indication for a tonsillectomy or an adenoidectomy is chronically infected tonsils; tonsillectomy might be considered in order to remove this source of chronic infection. Nine times out of ten the child under 3 years of age who has had his adenoids and tonsils out is an allergic child; it is possible to diagnose allergy in such a child on this basis.

One of the most important things in the management of the asthmatic child is a detailed history, which pinpoints, if anything does, etiological factors which may be present. We might obtain a history that the child only gets asthma during a certain season of the year; this indicates a seasonal asthma probably due to some pollen. Asthma which begins in the fall and lasts all winter indicates the possibility of a dust allergy or possibly a bacterial allergy.

Frequently, environmental control will be all that is needed to control the asthma if we learn from the history that such an etiological factor as a pet is possible. It may be the child has had no asthma until a pet has been

brought into the home; no allergic child should ever have a fur-bearing or feather-bearing pet. He should confine his pets to goldfish and turtles; one patient of mine has a snake.

Because a child spends about half his life in his bedroom it is important that the bedroom should be the room where most environmental control is practiced. In other words, he should live in what would be considered a cell block; he should have nothing in his room except his bed, a foam rubber pillow properly covered with a nonallergenic cover since even rubber pillows collect dust, and a rubber mattress likewise covered with a nonallergenic cover. Drapes, if they are put up, should be those that can be easily taken down and washed, such as nylon curtains. Any rugs should be small and easily washed. Toys should be kept in another room; there should be no pennants or pictures which are notorious for collecting dust, nor should there be books. Some allergists feel that the family should also take precautions throughout the house, but I feel that if we control the bedroom we have done about as much as we can expect a parent to do and still live a civilized life.

If the child does not improve on a regimen of environmental control and other previously mentioned measures, then he should be subjected to a certain number of skin tests, the injected antigens to include many of the common inhalants around the home (house dust, wool and feathers, and pyrethrum or other insect sprays), as well as pollens (spring pollens such as trees and grasses, fall pollens such as ragweed). Foods play a role in the etiology of asthma, but that they should be included in the skin tests is a controversial question. It is true that not many foods showing positive skin tests have been shown to be true etiologic factors; nevertheless every once in a while, a positive skin reaction to a certain food gives us a clue as to why the child is not doing well otherwise. Although this happens infrequently it happens often enough so that most of us include many of the common foods in our skin testing.

When we think we have found the etiologic agents, then what should we try? If we can eliminate certain environmental agents, we do. This might include removing all the feathers from the house, for example. Next, if there are foods we feel are the cause, we can eliminate those readily from the diet. If the etiologic factor seems to be dust, this is a more difficult problem since we can eliminate only a certain amount of dust in the house. The same is true of the pollens in the out-of-doors where it is impossible to get rid of them; although there are filters which can remove pollens from air entering the house, still the child cannot stay indoors all the time. This is also true of molds which are prevalent both indoors and out; it is impossible to eliminate them entirely. Their number can be reduced by dehumidifying and heating the inside air.

When we desensitize a child against dust and molds, for example, we also

feel that if he has a marked reaction to pollens, even though he has no trouble in the summer, these antigens should be included in the injections. The reason for this is that a great number of these children, about 60 per cent, will, if they have a positive ragweed skin test, eventually develop ragweed pollenosis, hay fever, or asthma. This practice does not require an additional injection, and will probably save the child extra time lost from illness later on.

The asthmatic child, just as the normal child, should be immunized against poliomyelitis, smallpox, diphtheria, tetanus and whooping cough. Some physicians hesitate to give these injections to the asthmatic child because of untoward reactions, but he needs protection as much as, or probably more than, the average child.

It has been said that the asthmatic child gets colds more frequently than the nonallergic child; this is questionable. What we think to be a cold may be an allergic rhinitis due to an inhalant or food; it has never been clearly differentiated whether these nose colds are really allergic or viral in etiology. I think we do feel that a virus disease in an asthmatic child probably may be both more severe and more prolonged than in the nonallergic child; certainly it often initiates the asthmatic attack. Consequently, I think it is probably wise to administer what viral vaccines we have, such as the influenza vaccines, and as more vaccines are made available, these also might be very helpful. Well controlled double-blind studies have shown that gamma globulin is of no use in such a child.

We give bacterial vaccines to almost every patient in our clinic. These have never been proven useful although there is a feeling among allergists that they do help; we are old-fashioned enough to think that they help. Some centers use nothing but autogenous vaccines. Dr. Crump, in Philadelphia, performs a bronchoscopy on every patient, and the secretions obtained are cultured. The children are then treated with nothing but autogenous vaccine made from these cultures. Dr. Crump's results are as good as those of anyone else.

The prophylactic use of antibiotics over a long period of time has also not proven very effective and has been abandoned. When we do use antibiotics, we use them at the onset of a respiratory infection—this may abort an asthmatic attack.

Physiotherapy is used a great deal in England with fairly good results; this is one field we in America have to explore more. Teaching these children how to expand their lungs and how to use their extra respiratory reserve when necessary I think might be very helpful.

With all this we still have about 5 to 10 per cent of asthmatic patients who do not do very well. Psychotherapy will help some of these. Whether these children are upset emotionally because of their disease or whether

the disease is such because of their emotions we do not know. However, a certain percentage of asthmatic children who do not respond to the ordinary orthodox treatment do get some help from psychotherapy; we are quite pleased with some of the results we have gotten with children in our clinic. Finally, we still have about 4 to 5 per cent who despite adrenal cortical steroid therapy, psychotherapy, and long-range orthodox treatment continue to do poorly; this is the group, I think, on which we should focus our attention, because they are the ones we have really been unable to help.

The Editor's Column

Delinquent Behavior: Medical Participation in Programs for Its Control

Behavior of an asocial character on the part of a minor reaches the Court when there is conflict with legal regulations. There are wide variations of misbehavior prior to this when truancy occurs, family and school control is lost, or other acts are committed contrary to the usual social setting. Such a situation is akin to physical disease since it demands exclusion from freedom of movement or confinement to an institution. Such occurrences may be related to only one individual or, on the other hand, may be manifested in an epidemic form as illustrated by gang behavior. The latter is usually related to lower social status, cultural environment, ethnic confusion and economic deprivation.

Two approaches for handling the potential delinquent become apparent: 1) individual evaluation, and 2) community programs. Delinquent behavior is an illustration of a highly developed mental illness not dissimilar to metabolic problems, infectious diseases or genetic deficiencies. The approach is not only toward a diagnosis of such behavior, but also toward the more specific causative factor or factors. Prevention is based on the evaluation of such things as parental attitudes (family stability, indulgence, privation, etc.), personality development and school adjustment. In addition to these individual items there is the broad problem of social status related to cultural background, ethnic grouping and economic needs.

With the apparent increase in the number of delinquents, the question naturally arises as to *who* will help effect a reduction in their numbers and *how?* The *who* is everyone, professional and lay. *How* becomes the responsi-

bility of medicine, religion, social services, and education. Government, Federal and State, can only supply funds and occasionally personnel (which are funds in kind). Voluntary agencies and teaching clinics with their multidiscipline personnel must assume a proportion of this load; medical participation is a necessary part of such programs.

Medicine, as represented by the obstetrician, pediatrician and general practitioner, has the first opportunity to become involved in the future upbringing of the child. A statement made by Aristotle many centuries ago is pertinent: "He who sees things from the beginning has the best view of them." The children's doctor, into whose care the newborn falls, has the privilege to share with the parents the responsibility for both his physical and emotional needs throughout the period of his personality development until maturation. The physician must recognize his limitations in specific instances and use related disciplines as he would in calling a surgeon for a patient with abdominal pain. In the broadening horizon of child practice, improved educational programs are being devised to increase our knowledge of "why children act as they do." Advantage should be taken of these facilities.

In addition to the individual responsibility of the physician to his patient, another privilege is offered in volunteer programs dealing with community problems. The physician's knowledge of realistic approaches makes him an essential member of a planning and policy body. When research and multidisciplinary action are coordinated, delinquency will join tuberculosis and venereal disease as examples of individual and community programs resulting in control.

PRESTON A. MCLENDON, M.D.

Book Reviews

Textbook of Otolaryngology. By DAVID D. DEWEESE, M.D. and WILLIAM H. SAUNDERS, M.D., 464 pages, 354 illustrations, St. Louis: The C. V. Mosby Company, 1960, $8.75.

This is a textbook primarily aimed at the beginner in the field; it is a simplified, well outlined book which covers the subject matter well but not in too great detail. Illustrations and diagrams are well done, adequately labeled and occur in sufficient numbers. The text is organized nicely and presented in very readable print. Details are accurate and suggestions practical.

Among the outstanding features of the book are the excellent illustrations of instrumentation and examination; procedures are pictured in detail and with effective use of close-up photography. Index, table of contents, and bibliography are more than adequate. This book is highly recommended for the student of otolaryngology; it will also serve as an occasional reference for the more active practitioner.

ROBERT SCHARF, M.D.

Human Toxoplasmosis. Proceedings of the Conference on Clinical Aspects and Diagnostic Problems of Toxoplasmosis in Paediatrics. Edited by J. Chr. Siim, M.D., 220 pages, illustrated, Baltimore: The Williams & Wilkins Co., 1960, $12.50.

This is a book born of an international conference held in 1956. It was revised and edited in 1959, but the end product has much the flavor of a conference. This is to the good and to the bad.

It is at least distracting that one of the presentations remains an abstract with an apologetic note "complete manuscript not received."; that some sections are translations of the original presentations in poorly corrected English; and that the introduction in French is not translated. Further, there is the inevitable overlap of multiple presentations from miscellaneous sources. However, the latter is also a contribution for the reader interested in details of the problem of toxoplasmosis.

All aspects are covered in papers by the world's authorities on the subject. Of greatest help to the pediatric clinician are Eichenwald's chapter on congenital toxoplasmosis and Siim's chapter on acquired toxoplasmosis. Here the clinical variants are described and the diagnosis discussed. Unfortunately treatment can be considered only experimental and the epidemiology not established. Thus prevention is poorly defined.

ROBERT H. PARROTT, M.D.

Infectious Diseases of Children. By SAUL KRUGMAN, M.D. and ROBERT WARD, M.D. Second edition, 398 pages, 55 illustrations and 7 color plates, St. Louis: The C. V. Mosby Company, 1960, $13.00.

To compile and then to keep updated a text on infectious diseases in children demands the zeal of—well, of Krugman and Ward. They have done it and done it well.

The second edition, two years after the first, has all the plusses of the earlier volume and is as up to date as it is possible to be with a text. The subjects are arranged alphabetically—a drawback to orderly clinical diagnostic thinking in this reviewer's mind—and primarily by etiologic categories rather than syndromes. Six syndromes are given separate chapters: The Common Cold, Viral Encephalitis, Aseptic Meningitis, Bacterial

Meningitis, Acute Respiratory Diseases and Acute Exanthems. In general, the chapters are a blend of the basic science background with practical clinical data and specific therapeutic guides as well as therapeutic principles. Pictures and charts are used tellingly. Useful references are given.

This reviewer might wish (a) in the realm of opinion, that consideration had been given in the chapter on "The Common Cold" to the idea that this syndrome might represent a bodily response to any of several viral agents rather than principally to the unitarian theory; (b) In the realm of being current, that there were some "stop the presses" mechanisms that would have allowed respiratory syncytial virus to be mentioned as a major cause of bronchiolitis; (c) In the realm of philosophy, that the authors, who have made some great strides against rubella themselves, in a pediatric textbook would have presented some of the "positive" aspects of the question of rubella in pregnancy. Most of their reasons mentioned for considering abortion are "psychological, sociological" . . . "The woman may be reluctant to face this potential calamity." It would be refreshing more often, particularly in a pediatric discussion of this subject, to see such thoughts as the 80 per cent chance of a perfectly normal baby, the new approaches to congenital heart disease and deafness and even cataracts, or at least some mention of the difficulty of diagnosing rubella or the question of the right and wisdom of a human physician to recommend abortion.

But this review is not intended at all to be destructively critical. After all, this reviewer has a copy at his right hand at all times. In his opinion, so should every practicing or teaching pediatrician.

ROBERT H. PARROTT, M.D.

The Royal Edinburgh Hospital for Sick Children, 1860–1960. By DOUGLAS GUTHRIE with various contributors, 87 pages, 34 illustrations, Edinburgh and London: E. & S. Livingstone, Ltd., 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents, $4.25.

This interesting and well written book describes the founding and subsequent development of "Sick Kids": the first Children's Hospital in Scotland and the second in Great Britain. It is salutary to have recalled to us the vicissitudes which have accompanied its development. Its founding was opposed by many who thought infants and children were adults in miniature and should be treated as such. Pediatricians were derided before they established their proper recognition by their colleagues. The ultimate success of this hospital as unfolded in the account of its growth, its development and the improvement in the standard of the health of the city's children, should give encouragement to those who are now contending with comparable opposition to the establishing of pediatric surgery as a specialty.

NEVILLE K. CONNOLLY, M.D.

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